Nanoparticles for Post-Infarct Ventricular Remodeling

Caijuan Dong[1], Aiqun Ma[1,*], Lijun Shang[2,*]

[1]Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China; [2]School of Chemistry and Biosciences, University of Bradford, Bradford, BD7 1DP, UK

*corresponding authors: Lijun Shang: l.shang1@bradford.ac.uk; Aiqun Ma: maaiqun@medmail.com.cn

Abstract: In recent years, tremendous progress has been made in the treatment of acute myocardial infarction (AMI), but pathological ventricular remodeling often causes survivors to suffer from fatal heart failure. Currently, there is no effective therapy to attenuate ventricular remodeling. Recently, nanoparticles-based drug delivery system is widely applied in biomedicine especially in cancer and liver fibrosis, owing to its excellent physical, chemical, and biological properties. Therefore, using nanoparticles as delivery vehicles of small molecules, polypeptides, *etc* to improve post-infarct ventricular remodeling are expected. In this review, we summarized the updated researches in this fast-growing area and suggested further works needed.

Keywords: myocardial infarction; heart failure; post-infarct ventricular remodeling; mechanism; inorganic nanoparticles; liposome; extracellular vesicles; drug delivery; engineering; biomarker

Introduction

With an aging population and the rising incidence of cardiovascular diseases such as hypertension and coronary heart disease, the prevalence of heart failure is gradually increasing. In 2013, 1 in 9 death certificates (284,388 deaths) in the United States mentioned heart failure, with heart failure being the primary cause in 58,309 of those deaths [1]. In China, the prevalence of heart failure is around 0.9%, and coronary heart disease is the major cause.

Primary myocardial damage (including ischemic myocardial damage like myocardial infarction, and immune myocardium damage like myocarditis) and cardiac overload (including pressure overload and volume overload) can impair heart muscle, resulting in compensatory changes such as ventricular hypertrophy or ventricular enlargement, known as “ventricular remodeling”. In this process, the heart's geometry, cardiomyocytes, interstitial components, and the phenotype of cardiomyocytes undergo a series of pathological changes. Ventricular remodeling is the basic mechanism of heart failure and has three main characteristics: 1) pathological cardiomyocyte hypertrophy accompanied by re-expression of embryonic genes; 2) myocytes death; 3) excessive fibrosis or increased degradation of myocardial extracellular matrix. In recent years, the molecular mechanism of ventricular remodeling has been studied mainly from the following aspects: (1) myocardial hypertrophy; (2) fibrosis; (3) inflammation; (4) mitochondrial dysfunction; (5) autophagy/apoptosis. We may slow the progression of cardiac remodeling by targeting the above mechanisms, thus

benefiting heart failure patients.

Nanoparticles refer to particles smaller than 100nm in at least one dimension. Due to its small size and excellent thermal and electrical properties, nanoparticles are now widely applied into biomedical and industrial fields such as aerospace, electronics, cosmetics, food additives and optical devices [2]. Meanwhile, considering inherent nanometer size of living cells' biological components, nanotechnology is being considered in various medical fields such as oncology and cardiovascular medicine. Nanoparticles as delivery vehicles of proteins, nucleic acid and small molecules may potentially provide sustained treatment in damaged tissues. Basic research showed that nanoparticles packed with Nox2-NADPH oxidase siRNA, insulin growth factor-1 (IGF-1), or pitavastatin enhanced cardiac function post MI [2-4], suggesting the infinite possibilities of nanoparticles in the treatment of post-infarct ventricular remodeling.

In this review, we first introduced the present understanding of mechanism of ventricular remodeling and new advances of drugs for ventricular remodeling, then focused on the most commonly used nanoparticles in cardiovascular disease, especially for post-infarct ventricular remodeling. We also briefly touched on nanoparticles used as diagnostics/biomarkers for cardiovascular disease, and engineering of nanoparticles for tailored and directed use, which are both growing rapidly in the area.

1. The mechanism of ventricular remodeling

1.1 myocardial hypertrophy

Myocardial hypertrophy is a powerful adaptive form for various causes of cardiac output reduction, but it is not infinite. If pathological factors last for a long time, the function of the hypertrophic myocardium cannot be maintained persistently and eventually turns to heart failure. At present, plenty of studies support that APJ receptor plays a significant part in cardiac hypertrophy [5]. The hypothesis has been raised that APJ internalization via clathrin-mediated endocytic pathway may contribute to myocardial hypertrophy. As the molecular mechanisms of cardiac hypertrophy have been widely studied，the role of long non-coding RNAs (lncRNAs) has become more prominent [6]. The lncRNA Mhrt (myosin heavy chain-associated RNA transcript) is shown to affect cardiac hypertrophy remodeling by affecting the acetylation of myocardin, a substance which is necessary for programming cardiac muscle [7].

1.2 Myocardial fibrosis

Myocardial fibrosis is known for excessive accumulation of extracellular matrix in the myocardium, which a basic component for most cardiac pathologic changes [8]. Fibrotic cardiac muscle is stiffer and less compliant, causing ventricular systolic and diastolic dysfunction.

1.2.1 Changes in extracellular matrix components (ECM)

Myocardial extracellular matrix is composed of collagen, proteoglycans, glycoproteins, glycosaminoglycans, and elastic fibres, which are synthesized and secreted by cardiac fibroblasts. These components are essential for the nutrition and conduction of myocardium, and the normal structure and function of heart. Under the condition of ischemia and hypoxia, cardiac fibroblasts will move to the injured site, and produce a large amount of extracellular matrix under the mediation of various cytokines and neurohumoral factors. Epicardium-derived cells, but not bone marrow-derived blood cells, are the main origin of cardiac fibroblasts in the infarcted heart [9]. Significantly, differentiated states of fibroblasts are of importance to post-infarct ventricular remodeling of scarring. Fibroblasts were activated and highly proliferative, reaching a maximum rate within 2 to 4 days after MI. Up to 3 to 7 days, these cells differentiated into myofibroblasts and expressed smooth muscle α -actin to structurally construct the infarcted zone. As the scar completely formed (around 7-10 days), myofibroblasts gradually lost proliferative ability and smooth muscle α -actin expression [10]. This suggests that these fibroblasts might be a target of nanoparticle-mediated drug delivery system.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases which can degrade ECM. According to their structure and substrate selectivity, MMPs can be roughly classified into collagenase, gelatinase, matrix lysin, membrane-type metalloproteinase and

others. Under normal conditions, MMPs are mostly in the form of zymogens, with low expression levels and weak activity. Once activated under the stimuli of various pathological factors, such as ischemia and hypoxia, MMPs rapidly participate in the degradation of ECM and modulate the signaling pathways related to vascular remodeling and myocardial fibrosis. It has been shown that elevated MMP-9 levels are associated with left ventricular dysfunction and targeted knockout of mouse MMP-9 gene can decrease collagen accumulation post MI and attenuate left ventricular dilation [11].

1.2.2 Disproportionality of myocardial collagen fibre

Fibrillar collagen is the major structural protein of cardiac extracellular matrix. It is generally classified into type I (approximately 85%), type III (about 11%), and quite less abundant types IV, V and VI. Collagen types I and III have their own functions, that is collagen type I is responsible for building thick fibres which maintain its tensile strength, while collagen type III is in charge of constructing thin fibres which keep elasticity of the matrix [12]. Changes in the number, distribution, and arrangement of collagen fibers can lead to fibrosis. Cardiac fibroblasts are the major source of collagen fibers in the myocardial infarction. As the most frequently used marker of myocardial fibrosis, collagen peptides can predict cardiac function. For instance, the most common marker of type I collagen is a 100 kDa, C-terminal polypeptide whose plasma levels are positively correlated with diastolic dysfunction; the most commonly used marker for the synthesis of type III collagen is a 42-kDa, N-terminal polypeptide, whose plasma levels are positively associated with mortality and heart failure

[13, 14].

1.3 Inflammation

Inflammation plays a vital role in ventricular remodeling, and its lasting activation may result in irreversible cardiac damage. Activation of multiple inflammatory factors and signaling pathways have been mentioned in patients with heart failure [15]. Inflammatory molecules involved in ventricular remodeling mainly include TNF-α, IL-6, IL-10, IL-18 and nuclear factor-κB. Under the chemotaxis of multiple cytokines, monocytes are recruited to the cardiac tissue from circulation, and then they differentiate into macrophages and contribute to tissue injury and myocardial fibrosis [16]. Infarct macrophages exhibit inflammatory "M1" phenotype early and reparative "M2" phenotype later after MI [17]. Numerous studies have shown that the shift from M1 to M2 macrophages can improve post-infarct ventricular remodeling. Future studies can be aimed at targeting specific harmful functions while preserving beneficial effects of macrophages to prevent adverse cardiac remodeling.

NLRP3 inflammasome is a large molecule polyprotein complex, a component of the innate immune system. It is of great importance in both aseptic and infectious inflammation and can be activated by a variety of endogenous and exogenous factors. Studies have revealed that NLRP3 is closely associated with the pathogenesis of heart failure. When the myocardium is in a state of ischemia, NLRP3 is activated, producing IL-1β and IL-18. IL-1β further activates nuclear transcription factor (NF-κB). In turn, activation of NF-κB can also induce the

expression of precursors such as IL-18 and IL-1β. IL-18 is associated with the expression of collagen types I and III in a dose-dependent manner and induces myocardial remodeling and interstitial fibrosis.

1.4 Mitochondrial dysfunction

Mitochondrial dysfunction may potentially participate in almost all the mechanisms involved in ventricular remodeling [18]. Varieties of studies have demonstrated that there are functional defects of electron transport chain and oxidative phosphorylation complex in myocardial mitochondria during heart failure. In animal models of heart failure, the activity of myocardial mitochondrial complex IV is significantly reduced and the activity of complex I and III are inhibited. These changes not only reduce mitochondrial ATP synthesis but also increase mitochondrial ROS production. ROS modifies the myofibrillar protein of the myocardium through oxidation, resulting in the progressive reduction of cardiac contractility and irreversible cardiac damage [19].

In addition, angiotensin II (Ang II) destroys myocardial mitochondria by increasing the production of reactive oxygen species (ROS) and interferes with mitochondrial oxidative phosphorylation, including fatty acid oxidation [18, 20]. Fatty acids are the main energy substrate of the heart and offer most cofactors essential for mitochondrial oxidative phosphorylation. Studies have shown that overexpression of angiotensinogen in transgenic mice (TG1306/R1 mice) can reduce cardiac fatty acid oxidation and expression of PPARα

protein and fatty acid oxidase [21].

1.5 Autophagy and Apoptosis

Autophagy is the decomposition process of proteins and organelles. It is characterized by the encapsulation of cytoplasmic proteins or organelles to form autophagosomes with a bilayer membrane structure. Autophagosomes fuse with lysosomes to form autolysosomes. The parcels are decomposed into small molecules such as free amino acids and fatty acids and be recycled [22]. Macroautophagy, microautophagy, and chaperon-mediated autophagy all allude to autophagy, but here autophagy refers to macroautophagy [23]. Cardiomyocyte autophagy plays a prominent role in maintaining the stability of internal environment, and the structure and function of heart. Ischemia induces autophagy in cardiomyocytes. Kanamori first reported that autophagy was rapidly activated in cardiomyocytes within 30 minutes after coronary ligation, and strong autophagic activity was observed particularly in saved cardiomyocytes around the infarcted zone [24]. His following study found that autophagy inhibitor chloroquine can reduce myocardial autophagy and aggravate ventricular dilatation and myocardial remodeling, suggesting that autophagy plays a protective role in post-infarct ventricular remodeling [25]. There are two main pathways for the regulation of myocardial cell autophagy: 1) mTOR-dependent pathway; 2) Beclinl-dependent pathway. Among them, the mTOR-dependent pathway plays a major role in post-infarct ventricular remodeling. mTOR,a serine/threonine protein kinase, is proved to regulate autophagy. Increased mTOR activity inhibits autophagy, while decreased mTOR activity activates autophagy [26].

Necrosis has been considered as the only cause of myocyte loss in MI for a long time. However, mounting evidence suggests that apoptosis plays a critical role in the progression of post-infarct ventricular remodeling and heart failure, too. Cardiac-specific caspase-3 is the most important caspase in the terminal apoptotic pathway in the infarcted heart. The study found that overexpression of caspase-3 increased infarct size in transgenic mice [27]. Vice versa, reduced caspase-3 narrowed the infarct size, lowered the number of apoptotic cardiomyocytes and promoted the cardiac function in MI mice [28, 29]. One study from Zhou *et al.* found that isoproterenol induces abnormal endoplasmic reticulum stress through inactivation of AMPK, which in turn damages cardiomyocytes, causes apoptosis, and leads to heart failure in rats, and all the processes can be suppressed by activating AMPK, providing a potential mechanism of apoptosis [30].

In conclusion, none of the above processes is independent. On the contrary, they interact with each other and form a complex mechanism network. Nanoparticles loaded with the drugs targeting any of these mechanisms are expected to reverse ventricular remodeling and prevent further progression of the disease. We summarized the mechanism of ventricular remodeling in Figure 1.

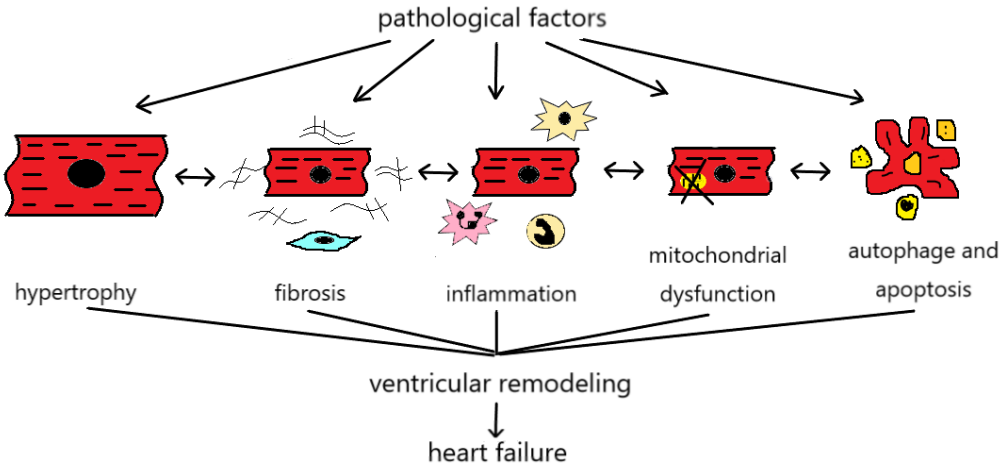

FIGURE ： The mechanism of ventricular remodeling. Hypertrophy、fibrosis、inflammation、mitochodrial dysfunction、autophage and apoptosis are involved in the pathways of ventricular remodeling.

2. Nano- cargo for ventricular remodeling

Drugs, proteins, RNA and other small molecules all can be the cargo of nanoparticle-based drug delivery system, which we describe below in details.

2.1 Drugs

We summarized new advances of drugs for ventricular remodeling in Table 1. The recent development of cardiovascular medicine and coronary intervention like PCI greatly decreased the mortality of AMI, but the incidence of chronic heart failure patient's post MI is increasing. Nanotechnology-based drug delivery system (nano-DDS) is a hot topic in drug delivery and has been successfully adopted in cancer therapy. Besides higher biocompatibility, Nano-DDS can increase the precision of drug targeting and the level of drug accumulation in the desired

area, which will be discussed in detail in later sections. Therefore, nano-DDS has great potential in cardiovascular diseases. As is known to us all, statins have anti-inflammatory effects. Shunsuke Katsuki *et al* utilized PLGA as the carrier of Pitavastatin and tested its efficacy in MI model. They found intravenous treatment with PLGA-Pitavastatin nanoparticles attenuated post-infarct ventricular remodeling by interfering with monocyte recruitment and reducing monocyte/macrophage accumulation in the heart. This indicated that inflammatory cells might be the target of PLGA-Pitavastatin nanoparticles [31].

However, not all the drugs can be nanoparticulated in view of size and structure. Furthermore, there are few animal studies using nanoparticles in the treatment of heart diseases, albeit clinical trials. For example, Zhang, *et al* showed size-dependent cardiac effects of gold nanoparticles in isoproterenol-induced hyperthyroid rats, suggesting that size is an important factor affecting safety and efficacy of nano-DDS [32]. Further extensive work is needed to explore the target cells and examine the efficacy and safety of these cardioprotective drugs with nano-DDS before going into clinical trials.

Table1. New advances of drugs for ventricular remodeling

Classification	**Typical Drugs**	**Function**	**References**
Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors	Aliskiren, Aldosterone, Eplerenone	Inhibit cardiac hypertrophy and reduce the proliferation of extracellular matrix and interstitial fibrosis.	Gheorghiade M, *et al* [33] Dhillon S, et al [34]

β-Adrenoceptor Blockers	Atenolol, Metoprolol Tartrate Tablets , Propranolol	Block the sympathetic nervous system, RAAS system and reduce oxygen consumption of heart muscle.	Xie M, et al [35]
Hydroxy-3-methyl-glutaryl Coenzyme A (HMG-CoA) Inhibitors	Atorvastatin、rosuvastatin	Inhibit oxidation and inflammation, reduce sympathetic nerve activity, and improve vascular endothelial function.	Duan H Y, et al [36] Mahalwar R, et al [37]
Vascular Endothelin-1 (ET-1) Receptor Antagonists	Bosenta, Enrasentan, Tezosent, Sitaxentan, Atrasentan, Ambrisentan	Contract blood vessels, promote cell mitosis and proliferation.	Prasad S K, et al [38]
New vasodilators	Sildenafil, AVE9488	Inhibit cardiac hypertrophy, apoptosis and fibrosis	Vecchis R, et al [39] Fraccarollo D, et al [40]

2.2 Proteins

We summarized some proteins which contribute to cardiac repair and attenuate adverse remodeling in Table 2. Under ischemic conditions, certain proteins can play important roles in attenuating and delaying pathological ventricular remodeling. However, their effect is quite limited as a result of short half-lives *in vivo* in their free form. What if they are nanoparticulated? In fact, some of them have been nanoparticulated for use in the treatment of post-infarct ventricular remodeling in animal experiments. For example, injecting PLGA-IGF-1 nanoparticles into the myocardium of MI mice was effective to narrow infarct size, prevent cardiomyocyte apoptosis, and improve left ventricle ejection fraction three weeks after the left coronary ligation surgery [3]. But similar animal studies are still lack, and transition from basic research into clinical trials is near to zero. Future studies should focus on

this part of works and provide more reliable data.

Table 2. New advances of proteins for ventricular remodeling

Proteins	**Cardioprotective effect**	**References**
Vascular endothelial growth factor (VEGF)	Promote cardiac stem cells differentiation into vascular endothelial cells.	Xiao N, et al [41]
Insulin-like growth factor-1 (IGF-1)	Promote stem cell growth and differentiation.	Jackson R, et al [42]
Thymosin β4	Promote neoangiogenesis and cardiac regeneration.	Srivastava D, et al [43] Shrivastava S, et al [44]
Fibroblast activation protein alpha(FAP)	Promote fibroblast migration	Tillmanns J, et al [45]
Hypoxia-inducible factor-1 alpha (HIF-1α)	Promote cardiac function, angiogenesis, cardiomyocyte proliferation, and reduction of fibrotic tissue with no induction of cardiac hypertrophy.	Cerrada I, et al [46]
Wnt1/βcatenin	Induces cardiac fibroblasts to proliferate and express pro-fibrotic genes.	Duan J, et al [47]
Transforming growth factor-β(TGF-β)	Activate a pro-fibrotic and matrix-preserving program in infarct fibroblasts through Smad-dependent actions.	Shinde AV, et al [48]

2.3 RNA

MicroRNAs (miRNAs) are small, noncoding, single-stranded RNAs, which can regulate the gene expression by interacting with target mRNAs and preventing them translating into functional proteins. It has been shown that miR-1, miR-21, miR145, etc modulated the gene

expression relative to ventricular remodeling. If these miRNAs are nanoparticulted and delivered to the infarcted heart, it may prevent adverse ventricular remodeling. In fact, extracellular vesicles are natural delivery vehicles of miRNA and have been used in the treatment of ventricular remodeling in basic research, which will be discussed in detail in later part. Other kinds of nanoparticles such as liposomes are also studied. For example, one study investigated that miR-145 encapsulated in liposomes was intravenously administered to MI rabbit and had a cardioprotective effect by inducing cardiomyocyte autophagy through targeting fibroblast growth factor receptor substrate 2 [49].

Small hairpin RNA (shRNA), an artificial RNA, is named for a tight hairpin turn that can be used to silence specific gene expression through RNA interference (RNAi) and reduce the level of targeted proteins. As an example, one study exhibited that rPEI/siRAGE showed high target gene silencing and low toxicity in cardiomyocytes, and the treatment of rPEI/siRAGE reduced the myocardial infarction size [50].

3. Nanoparticles for treatment of post-infarct ventricular remodeling

Heart failure post MI is an important component of cardiovascular related diseases. As mentioned before, the repair mechanism of post MI causes collagen scarring to replace damaged cardiomyocytes. The non-shrinkage of the scar leads to viable cardiac hypertrophy, thinning of the infarct wall and expansion of the ventricles, which is known as ventricular

remodeling. Without effective treatment, these processes will continue until the heart no longer adequately pumps enough blood to the body, which is defined as heart failure. At present, the drugs used for the treatment of heart failure only aim at its pathophysiological process, but do not target the cause. Worse still, the current available means of delivering cardioprotective drugs often misses the deadline of reversible repair of cardiomyocytes and inevitably, cardiomyocytes undergo a series of remodeling processes. Therefore, developing novel therapies to alleviate the negative left ventricular remodeling post MI is very important.

Nanoparticles refer to nanometer-sized particles. It is defined as particles smaller than 100 nm in at least one dimension. Due to its small size and excellent thermal and electrical properties, nanoparticles are now widely used in industrial and biomedical fields such as cosmetics, food additives, aerospace, electronics, and optical devices [2]. Considering the intrinsic nanometer size of the living cell's biological components, if nanoparticles are designed as delivery vehicles of a variety of growth factors, enzymes and small molecule, the modified nanoparticles may provide infinite possibilities in the treatment of cardiovascular diseases. In addition, nanoparticles can achieve controlled drug release by constructing a release system in response of internal stimuli such as pH, redox state and the presence of biomolecules as well as external stimuli such as light and magnetic field. One study showed that pH-sensitive mesoporous silica based nanoparticles (MSN) could be mostly taken up by tumor cells for their acidic environment due to hypoxia [51]. Similarly, an infarcted heart is also in an acidic environment under ischemic condition. pH-sensitive nanoparticles can also be designed to achieve controlled drug release. In addition, if the nanoparticles can only be opened by

specific enzyme which is limited to infarct heart, the controlled drug release can also be achieved. Currently, the most commonly used nanoparticles in cardiovascular research are inorganic nanoparticles, liposomes, and extracellular vesicles, which are discussed below.

3.1 Inorganic nanoparticles

Common inorganic nanoparticles include gold nanoparticles, silver nanoparticles, and silicon nanoparticles and so on. They are widely studied in basic research associated with cardiovascular diseases.

3.1.1 Gold nanoparticles

Gold nanoparticles (AuNPs) have great potential in the diagnosis and treatment of various diseases, owing to their superior physicochemical and pharmacological characters. In terms of physicochemical properties, AuNPs are inert, stable and biocompatible, which means low toxicity. Moreover, the surface of AuNPs can be retouched as we wish, to improve precision and safety of its application in clinical or research [52]. As for the preparation process, AuNPs are easy to prepare and functionalize, which may lower the production cost, and this obvious economic advantage will make them more available in clinical. Based on the above, AuNPs are a valuable candidate for many biomedical applications, such as drug delivery, cancer therapy and biomedical imaging. This part focuses on the previous studies of gold nanoparticles in drug delivery. One study showed that continuous injection of gold nanofibres combined with platelet-derived growth factor into the heart of rats could reduce myocardial

cell death and maintain systolic function post MI. Considering that heart failure is related to abnormal electrical function, modified nanofibers to couple the electrical property was studied. The result showed that ex-vivo pretreatment of mesenchymal stem cells (MSCs) using 5-azacytidine and AuNPs loaded with conductive nanofibrous construct could improve cardiomyogenic differentiation, thus resulting in protective effects on infarcted area [53]. Another study showed that PEG-coated AuNPs could attenuate β-adrenergic receptor-mediated acute cardiac hypertrophy and inflammation by inhibiting the expression of β1-AR and its downstream effectors IL-6 and ERK1/2 [52]. In conclusion, AuNPs have at least two functions for treating heart failure: one is used as drug vector, the other is used as anti-cardiac hypertrophy agents.

3.1.2 Silicon nanoparticles

Silicon nanoparticles are also drawing more and more attention. Porous silicon (Psi) shares the similar characters with gold nanoparticles such as nanoscale size, large surface area (>300 m2/g) and good biocompatibility and biodegradability [54, 55]. Besides, high degree of porosity (50-80%) and the unique chemical surface are two special features of Psi, which can promote the solubility of hydrophobic drugs and control the drug release. An *in vivo* experiment tested the biocompatibility of different sizes of thermally oxidised porous silicon (TOPSi) nanoparticles in the heart tissue. Obvious changes in cardiac function and other systems like the haematological system were not found before and after MI, demonstrating that TOPSi nanoparticles have good biocompatibility [56]. Other research concluded that

functionalized undecylenic acid thermally-carbonised porous silicon nanoparticles can improve their ability of accumulation in different cardiomyocytes (primary cardiomyocytes, non-cardiomyocytes, and H9C2 myocardium). It has also been reported that intravenous administration of peptide-modified nanoparticles in MI rats induced by isoproterenol, could increase the accumulation of nanoparticles in the heart up to 3.0 times at 10 minutes, revealing the potential therapeutic effect of these peptide-modified nanosystems in post-infarct ventricular remodeling. Therefore, we can confidently expect that the PSi materials modified with heart-targeting peptides and cardioprotective factors might serve as a promising approach to treating heart diseases.

Nanoparticles mentioned above are delivered by directly injecting into the infarcted heart or through the intravenous administration. Some studies also deliver nanoparticles orally. However, this route of administration can cause an undesirable systemic response for their inherent metabolic pathways. Currently, drug delivery using inhaled nanoparticles has demonstrated a promising future [57-59]. For example, inhalation of calcium phosphate nanoparticles (CaPs) bound to peptides targeting heart were investigated and no changes in blood pressure, heart rate, or respiratory function were observed [58]. Therefore, efforts to develop tailored approaches with engineering designs are a hot topic in the study, as described in below part 5.

It is worth noting that inorganic nanoparticles can also cause toxic effects in multiple organs.

Experiments conducted on murine macrophage cell lines have shown that AuNPs could affect the immune system. In this study, AuNPs successfully reduced activation of Toll-like Receptors-9 receptors, which in turn reduced the secretion of various interleukins (IL-6, IL-12) and TNF-α [60]. Silica nanoparticles can cause toxic effects, too. The elevated level of pro-inflammatory cytokines like IL-6 and IL-12 , increased inflammatory cells such as natural killer(NK) cells and cytotoxic T-cells, and up-regulated genes associated with inflammatory responses were observed when cells were exposed to silica nanoparticles [61]. Besides, the level of cTnT, a sensitive indicator of AMI, was significantly elevated in old rats exposed to aerosol of silica nanoparticles [62], which exhibited cardiotoxicity.

3.2 Liposomes

Liposomes are composed of single or multiple outer lipid bilayers and an inner aqueous compartment, thus endowed with special properties that can be combined with both hydrophobic and hydrophilic materials. The diameter of liposomes is usually 20 nm to 10 μm, and the thickness of phospholipid bilayer is around 4-5 nm. Microfluidic technology has gradually been employed for liposome preparation in place of conventional methods [63-65]. At present, PLA, PGA and PLGA are three popular materials for the preparation of liposomes. Initially, liposomes were used in surgical implants and tissue repair. They were then rapidly introduced into other medical fields such as abdominal mesh and drug delivery vectors due to their excellent biocompatible, biodegradable and nontoxic properties [66-68]. Another unique advantage of using PLA to make nanoparticles is flexibility. Its physical properties as well as

chemical properties are easily changed to obtain the desired pharmacokinetics and biodegradable properties [68, 69]. Nano-liposomes have been shown to transport many substances such as low molecular weight drugs, imaging agents, peptides, proteins and nucleic acids. They can slowly release the encapsulated drug, maintain a higher drug concentration in the target area, and increase drug efficacy. This ability can also be applied to delivery of cardioprotective agents to the infarcted heart.

3.2.1 RNA

Nox2-NADPH, the major source of ROS in the heart, is associated with ventricular remodeling. It has been reported that the expression of Nox2-NADPH is up-regulated in the infarcted myocardium and deleting the gene of Nox2 can reduce oxidative stress and prevent adverse post-infarct remodeling. Considered above, a study used acid-degradable polyketal particles as delivery vehicles for Nox2-siRNA and found that intramyocardial injection of Nox2-siRNA nanoparticles to the post-MI heart successfully prevented upregulation of Nox2 and dramatically improved cardiac function [2].

3.2.2 Proteins and peptides

A study reported that the amount of angiotensin II type 1(AT1) nano-liposomes clustered in the infarcted heart after day 1 accounted for almost half of the total amount accumulated in all organs, exhibiting superior cardiac-targeted capability [70]. IGF-1 (insulin-like growth factor-1), a kind of peptide, has been revealed to improving cardiomyocyte growth and

survival both *in vitro* and *in vivo*. An animal experiment showed that injecting PLGA-IGF-1 NPs into the myocardium of MI mice was effective in narrowing infarct size, preventing cardiomyocyte apoptosis, and improving left ventricle ejection fraction three weeks after the surgery [3].

3.2.3 Drugs

It's well known that inflammatory responses plays a critical role in the development of post-infarct remodeling [71]. For this reason, a study explored the effects of PLGA NPs combined with the anti-inflammatory drug-pitavastatin on post-MI mice and concluded that treatment with PLGA-Pitavastatin NPs alleviated post-infarct remodeling along with a reduction of monocytes/macrophages in the heart, yet the control group did not. Specifically, PLGA-Pitavastatin NPs not only prevented monocytes from mobilizing in the spleen in MI mice, but also decreased the amount of inflammatory cells in the infarcted heart in splenectomy mice4. This suggests that nanoparticles loaded with pitavastatin or other similar drugs may be a novel therapeutic strategy to protect the heart from inflammatory damage.

Compared with inorganic nanoparticles, there are few reports about the toxicity of liposomes. Lutein- PLGA nanoparticles were prepared and tested for acute, subacute toxicity, bioavailability and tissue distribution in mice. The results did not show any significant changes in mortality, hematology and other vital organs compared with the control group [72]. However long-term toxicity studies are needed.

3.3 Extracellular vesicles (EVs)

Extracellular vesicles which are of nanoscale size and surrounded by a phospholipid bilayer, are secreted by almost all cell types into extracellular space. EVs are originally considered as cellular debris, but more value in carrying and exchanging biological information is explored with the in-depth research. According to the vesicles' size, biogenesis and surface markers, EVs can generally be divided into exosomes, microvesicles/ectosomes and apoptotic bodies. Exosomes, roughly 30 to 100 nm in size, are derived from late endosomes. Microvesicles, ranging between 100 and 1000 nm, are generated by budding from the plasma membrane. Apoptotic bodies are derived from apoptotic cells and are more than 1000nm in diameter. However, due to the different methods of isolating and purifying vesicles, it is difficult to classify EV precisely. Clinical applications of EVs fall into two main categories: 1) EVs are used as biological drugs. Some of the molecules contained in EVs secreted by specific cells have therapeutic effects such as immunosuppression, immune activation, tissue repair and cardiac protection [73]. 2) EVs are used as the drug-delivery system. EVs can serve as a natural nano drug delivery system to deliver drugs to target cells. Currently, EVs have been used successfully as a carrier for the delivery of small molecules, siRNAs, proteins, and mRNAs for preclinical studies.

One study surprisingly found that although there are many kinds of cells in the heart tissue such as cardiomyocytes, endothelial cells and fibroblasts, EVs from CD34+ stem cells were

only selectively captured by cardiomyocytes and endothelial cells, indicating the existence of cell-specific receptors on EVs from CD34+ stem cells [74]. Increasing evidence has confirmed that EVs are enriched in microRNAs which regulate growth, proliferation and survival. More interestingly, microRNAs enclosed in different EVs are quite different from each other and perform different tasks. It has been demonstrated that cardiac progenitor cell -derived exosomal particles which contain miR-21 could prevent cardiomyocytes apoptosis [75]. Other similar studies investigated that miR-132 containing exosomes derived from pericyte had a pro-angiogenic capacity and miR-155 containing exosomes could mediate macrophage-fibroblast interactions and protect damaged myocytes by inhibiting fibroblast proliferation [76]. All of these highlight that understanding how EVs are released and taken up would help to manage and govern post-infarct ventricular remodeling. Future studies might aim at targeted delivery of EVs containing beneficial factors to heart. We summarized the latest findings of exosomes and their miRNAs on cardiac repair in Table 3.

Table 3. Exosomes and the miRNAs on cardiac repair

Cellular origins of exosomes	**Contained miRNAs**	**Mechanism**	**Cardioprotective Function**	**References**
Cardiac-derived progenitor cells	miR-1	Target and inhibit the expression of sprouty-related EVH1 domain-containing protein 1 (Spred1).	Enhance angiogenesis and potentially improve cardiac regeneration	van Mil A, et al [77]
Induced pluripotent stem cells (iPS cells), derived from somatic cells reprogrammed by four	miR-21, miR -210	Associate with Nanog, an embryonic stem cell-specific	Reduce oxidative stress and promote cardiomyocytes	Y Wang, et al [78]

stem cell transcription factors, Oct4, Sox2, Klf4, and c-Myc		transcription factor, and the key hypoxia related transcription factor HIF-1α.	survival	
mesenchymal stem cells (MSC) overexpressing GATA-4	miR-19a, miR-451	Activate the Akt and ERK signaling Pathways.	Reduce apoptosis	Bin Yu, et al [79]
human $CD34^+$ peripheral blood-derived hematopoietic stem cells	miR-126, miR-130a	Increase production of CXCL12 in endothelial cells and reduce protein levels of phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2)	Promote angiogenesis	Mocharla P, et al [80]
Mesenchymal stem cells	miR-22	Target methyl CpG binding protein 2 (Mecp2).	Reduce apoptosis and cardiac fibrosis	Y Feng, et al [81]
Saphenous vein-derived pericyte progenitor cells (SVPs)	miR-132	Inhibit Ras-GTPase activating protein and methyl-CpG-binding protein 2	Improve contractility, reparative angiogenesis, and interstitial fibrosis	Katare R, et al [82]

Compared with liposomes, EVs have the following characters. 1) EVs contain a lipid layer and have a better fluidity; 2) membrane proteins contained in the lipid layer of EVs are potentially targeted; 3) EVs can be modified to carry the required membrane fusion and cell-uptake devices; 4) EVs are similar to the body's own cells, so they are non- immunogenic and biocompatible; and 5) EVs are self-cell products which can avoid being degraded by macrophages, endosomal and lysosomal pathways. These natural features make EVs easier to be captured by target cells and enhance drug delivery efficiency, opening up new ways for drug delivery. However, there is still a long way to fully master physiological characteristics

of EVs and improve EVs isolation and drug loading techniques, finally realizing the changes from basic to clinical practice.

4. Nanoparticles used as diagnostics and biomarker for CVD

Nanoparticles are increasingly being recognized as markers of disease presence and prognosis like cancer and cardiovascular diseases [83, 84]. Previously noted, EVs are produced by budding from cytoplasm. Therefore, their contents indirectly reflect the type and condition of original cells. By detecting EVs in the serum, urine and other bodily fluids, we may identify the disease presence and evaluate prognosis. For instance, hypoxia and oxidative stress altered the proteomic and RNA content of endothelial and mast cells [85]. Increased microvesicle levels were found in acute coronary syndrome than that in-stable angina [84]. Some clinical research suggested that plasma levels of exosomes subtypes might be used as indicators of vascular endothelium damage in CVD，but more work needed in exploring the potential and attractive ability of EVs.

5. Engineering precision nanoparticles for personalized cardiovascular diseases

Current efforts in nanoparticle work develop increasingly towards tailored approaches and for this purpose nanoparticles, including extracellular vesicle therapy for heart disease, are being

modified more and more, such as Enzyme Prodrug Therapy (EPT) and Microfluidic technology. EPT makes it possible to release drugs in desired positions by converting inactive prodrugs to active drugs with the participation of enzymes [86]. Microfluidic extrusion approaches for fabricating exosome mimetics from donor cells and microfluidic surface engineering of living-cell-derived exosomes are two research direction in microfluidic technology, but still face lots of challenges [87]. Magnetically sensitive microcapsules have provided a novel method of targeted cell delivery. Magnetically sensitive cells which contain magnetic nanoparticles in their walls can transfer to the desired sites and repair the damaged tissue in applied magnetic field [88]. However, there is almost no research on the application of magnetic sensitive microcapsules to cardiovascular diseases.

6. Conclusion

Cardiovascular disease (CVD) is one of the leading causes for death. Although great advances of therapy strategies have been achieved in acute myocardial infarction in recent years, pathological ventricular remodeling often causes survivors to suffer from fatal heart failure. Nanoparticles as emerging drug delivery vehicles are drawing more and more attention, especially in cardiovascular areas. In this review, we summarized current knowledge about nanomedicine for post-infarct ventricular remodeling, and described basic mechanisms of ventricular remodeling, including hypertrophy, fibrosis, inflammation, mitochondrial dysfunction, autophagy and apoptosis. A better understanding of the mechanisms would help

us to find new therapeutic targets for ventricular remodeling. We also listed potential nano-cargo such as drugs, proteins and RNA for post-infarct ventricular remodeling. Once nanoparticulated, these drugs, proteins and RNA might have a better cardioprotective effects. Furthermore, we summarized the characters of inorganic nanoparticles, liposomes and extracellular vesicles and listed their application in post-infarct ventricular remodeling. Nanoparticle-based drug delivery system shows high compatibility, low toxicity, high drug accumulation and controllable drug release. To broaden the knowledge about nanomedicine, we also briefly described engineering of nanoparticles.

7. Future Perspective

To date, nanoparticles packed with peptides, siRNA and other small molecules are observed to exert beneficial effects on damaged cardiac myocytes and the infarcted heart both *in vitro* and *in vivo*. What's more, nanoparticles are shown to be potential biomarkers of CVD. Nonetheless, there are still some problems in the application of nanoparticles for treating post-infarct ventricular remodeling: 1) Nanoparticles are lack of specific markers on targeting cardiac myocytes. It can cause drug accumulation in other relevant target organs and correspondingly produce toxic and side effects. 2) The study of nanoparticles for improving cardiac remodeling is lack of the combination of long-term and short-term animal experiments. The commonly accepted method for establishing the model of AMI in rats is left anterior descending artery ligation. The surgery is very demanding on the operator's skill and

is extremely traumatic for rats. Therefore, the long-term survival rate of rats (more than three weeks) is quite low. The future work should emphasize on the long-term animal experiments and investigate the long-term effects of nanoparticles to the infarcted animals. 3) There are few studies on the effects of nanoparticles on ion channels in cardiac myocytes. The ion channel is a popular and challenging topic in cardiac research. Do nanoparticles affect the ion channels in cardiac myocytes? If yes, what is the mechanism? This may be a direction for future research on nanoparticles. 4) There is still great technical difficulty and cost concerns in the ideal combination of drugs and nanoparticles. The nanoparticles need to be well engineered to achieve desired size, shape, surface charge, and other physicochemical properties, thus a complex and costly method are demanded. Incomplete characterization of nanoparticles can lead to various biological effects. In addition, materials with combination of less toxicity and side effects, better biocompatibility, and more controllable drug release will pose major challenges to the materials industry. 5) Nanoparticles for the treatment of post-infarct ventricular remodeling are still lacking clinical data. Current research in this area is still limited to animal and cell experiments and there are no reliable clinical trials to support the idea. More work is urgently needed to achieve clinical transition of nanoparticles. 6) 3D printing has gained a significant focus in biomedical and nanobiomaterials research. Future studies may adopt 3D printing technology in nanoparticle-based drug delivery system.

On a positive note, nanoparticles as the delivery vehicle of various drugs have already entered clinical research for the treatment of hepatic fibrosis and cancer. This brings hope to nanoparticles for post-infarct ventricular remodeling.

Executive Summary

Introduction

- The prevalence of heart failure is gradually increasing and ventricular remodeling is the major cause.
- Nanoparticles have great potential as drug delivery vehicles in post-infarct ventricular remodeling.

The mechanism of ventricular remodeling

- Hypertrophy, fibrosis, inflammation, mitochondrial dysfunction, autophagy and apoptosis are the basic mechanisms of ventricular remodeling.

Nano-cargo for ventricular remodeling

- Nanoparticulation of drugs, proteins and RNA is expected to treating post-infarct ventricular remodeling.

Nanoparticles for treatment of post-infarct ventricular remodeling

- Inorganic nanoparticles, liposomes and extracellular vesicles as delivery vehicles of RNA, protein, drugs，et al, have been studied in basic research in the treatment of post-infarct ventricular remodeling.

Nanoparticles used as diagnostics and biomarker for CVD

- Nanoparticles are increasingly being recognized as markers of presence and prognosis of cardiovascular diseases.

Engineering precision nanoparticles for personalized cardiovascular diseases

- Enzyme Prodrug Therapy (EPT) and Microfluidic technology increase the precision of

targeting.

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